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| 10/714,078 | 11/14/2003 | Gunars E. Valkirs | 36671-743.503 | 2621 |

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WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| COOK, LISA V | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/714,078 | VALKIRS ET AL. | |
| | Examiner | Art Unit | |
| | LISA V. COOK | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *32-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6/17/08 has been entered.

2. Claims 32-41 are pending and under consideration.

### *Information Disclosure Statement*

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

4. The information disclosure statement filed 6/18/07 has been considered as to the merits prior to Final Action.

5. The information disclosure statement filed 7/25/07 has been considered as to the merits prior to Final Action.

6. The information disclosure statements filed 6/17/08 have been considered as to the merits.

***Drawings***

7. No drawings were filed in this application.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 32 and 37-41 are rejected under 35 U.S.C. 103(a) as being obvious over Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and further in view of Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297).

Seilhamer et al. teach immunoassays utilizing antibodies that bind human, porcine and canine brain natriuretic peptides (BNP). See abstract, column 5 lines 54-62, and column 18 lines 50-60.

One useful antibody was specific for (binds to) SEQ ID NO:49 (BNP) and used in immunoassays. See claims. The antibody that binds SEQ ID NO:49 of US Patent #6,897,030 would also bind the 108 amino acid brain natriuretic peptide comprising SEQ ID NO:1, of the instant invention. More particularly, SEQ ID NO:49 is identical to amino acid numbers 77-108 of SEQ ID NO:1 (or the claimed BNP). Therefore, the antibody in US Patent #6,897,030 reads on the instant invention.

With respect to claims 40 and 41, the antibody recognizing the 108 amino acid BNP would necessarily recognize pro-BNP and NT-proBNP because the compounds all include BNP. Absent evidence to the contrary the antibody taught in US Patent #6,897,030 would recognize/bind all compositions including BNP.

Seilhamer et al. differ from the instant invention in not specifically teaching that the measured BNP could be used in the determination of stroke.

Nitta et al. teaches that plasma concentrations of brain natriuretic peptide are elevated in pre-hemodialysis patients with left ventricular dysfunction. For example, see abstract and page 415. Although Nitta et al. discuss the relationship between BNP and left ventricular dysfunction, the reference is silent with respect to stroke.

However, Kelly et al. teach that left ventricular dysfunction (LVSD) is found in patients with stroke (TIA). See page 295. " One might expect that about 10-35% of stroke/TIA/PVD patients have asymptomatic LVSD." See page 296 1st column. The measurement of BNP may reduce the number of patients needing echocardiograms, aide in identifying and treating LVSD to reduce the incidence of cardiac death. See page 296 2nd column.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the antibody detection procedure for BNP as taught by Seilhamer et al. and evaluate stroke because Nitta et al. taught that plasma concentrations of brain natriuretic peptide are elevated in pre-hemodialysis patients with left ventricular dysfunction and Kelly et al. taught that left ventricular dysfunction (LVSD) is found in patients with stroke (TIA). See page 295. The measurement of BNP may reduce the number of patients needing echocardiograms, aide in identifying and treating LVSD to reduce the incidence of cardiac death. See page 296 2nd column.

**II.** Claims 33 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and further in view of Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) as applied to claims 32, 37, and 38-41 above, and further in view of Jackowski et al. (WO 00/52476).

Please see Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and further in view of Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) as set forth above.

Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and further in view of Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) differ from the instant invention in not specifically teaching the evaluation of CT scans (claim 36) and multiple sample markers (claim 33).

However, Jackowski discloses method for assessing stroke (cerebral injury) via the measurement of multiple markers. The various markers include calbindin-D, myeline basic protein, S-100β, and thrombomodulin. See figure 2 for example.

On page 1, Jackowski discloses that stroke is routinely diagnosed with a CT scans to assess brain damage. See lines 18-29. The multiple markers may be determined in the same sample or from samples obtained at different time periods. See page 12 lines 3-16. This allows for patient analysis and monitoring. The detection of multiple markers can distinguish and/or differentiate between ischemic and hemorrhagic events.

This evaluation aids in patient treatment. Jackowski teaches the determination of a plurality of patient derived markers which are correlated to a subarrachnoid hemorrhage. See abstract, figure 2, and column 3-4, for example. See page 2 lines 11-22 and figure 2/6, for example.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate CT and multiple markers like calbindin-D as taught by Jackowski et al. in the method of Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and further in view of Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) because Jackowski et al. taught that the detection of multiple markers along with CT can distinguish and/or differentiate between ischemic and hemorrhagic events. This evaluation aids in patient treatment. See abstract, figure 2, and column 3-4, for example. See page 2 lines 11-22 and figure 2/6, for example.

One of ordinary skill in the art would have evaluated multiple markers and CT in order to assess and monitor brain damage and aid in patient treatment.

**III.** Claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being obvious over Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) and further in view of Velier et al. (The Journal of Neuroscience, July 15, 1999, Vol.19, No.14, pages 5932-5941).

Please see Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) as set forth above.

Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) differ from the instant invention in not specifically teaching the detection of additional markers like caspase-3.

However, Velier et al. disclose methods measuring caspase-3 after focal stroke. See abstract. A panel of antibodies is used to measure capase-8 and caspase-3 activity. See page 5935, 2nd column 3rd paragraph. Caspase-3 was found in neurons and microglia located in the core infarct after injury (stroke). See figure 5. The results suggest that the pattern of active caspase-3 expression within the cerebral cortex after stroke is dependent on both the duration and extent of ischemia, as well as reperfusion. See page 5939 2nd column.

A role for caspase activation in microglial cell death is suggested. The study of caspase may facilitate the development of therapeutics capable of ameliorating the incapacitating loss of function resulting from cerebral ischemia. See page 5940, 2nd column.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate casapse-3 in stroke as taught by Velier et al. in the method of Seilhamer et al. (US Patent #6,897,030 B2) in view of Nitta et al. (American Journal of Nephrology, 1998, Vol.18, pages 411-415) and Kelly et al. (Q J Med. 1999, Vol.92, pages 295-297) because Velier et al. taught that Caspase-3 was found in neurons and microglia located in the core infarct after injury (stroke). See figure 5.

The results suggest that the pattern of active caspase-3 expression within the cerebral cortex after stroke is dependent on both the duration and extent of ischemia, as well as reperfusion. See page 5939 2nd column.

One of ordinary skill in the art would have been motivated to evaluated caspase because Velier et al. taught this may facilitate the development of therapeutics capable of ameliorating the incapacitating loss of function resulting from cerebral ischemia. See page 5940, 2nd column.

The use of two known cerebral markers in combination to evaluate cerebral injury is obvious because expected beneficial results are evidence of obviousness. In re Skoll (CCPA 1975) 523 1392, 187 USPQ 481; Ex parte Luck (BPAI 1993) 28 PQ2d 1875. In this instance the use of multiple markers would provide multiple data for precise and accurate measurement of the cerebral injury.

A long line of cases have held that the mere use of different starting materials, whether novel or known, in a conventional process to produce the result one would expect therefrom does not render the process unobvious. For example see, *In re Surrey et al.* (CCPA 1963) 319 F.2d 233, 138 USPQ 67; *In re Kanter* (CCPA 1968) 399 F2d 249, 158 USPQ 331.

***Response to Arguments***

Applicants argument and amendment have successful eliminated the rejections of record under 112, 1st paragraph. However, the amended claims read on the cited prior art cited herein. In particular, the claims previously read on the measurement of a 108 amino acid BNP precursor or immunologically detectable fragments thereof. Currently, the claims not only read on the BNP precursor but one or more markers related thereto. As defined the specification on pages 5 and 6, section 0018; "related markers" refers to one or more fragments of a particular marker that may be detected as a surrogate for the marker itself.

***Double Patenting***

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 32-41 are provisionally rejected on the ground of nonstatutory double patenting over claims 68-74 of copending Application No. 10/371,149. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Both applications are drawn to methods measuring the 108 amino acid BNP precursor as an indicator of stroke.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

***Response to Arguments***

Applicants contend that a terminal disclosure (TD) is not required at this point in prosecution, accordingly the rejection is maintained.

11. For reasons aforementioned, no claims are allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*Lisa V. Cook*
*Patent Examiner*
*Art Unit 1641*
*Remsen 3C-59*
*571-272-0816*

/Lisa V. Cook/
Examiner, Art Unit 1641